The Position of the Examiner

The Examiner's position regarding the Chu reference has been previously made of record. In summary, the Examiner states that Chu discloses an analytical device and method of making the device, where the device comprises a porous reaction membrane and at least one receptor immobilized in a limited region, and where a surfactant is applied to the reaction membrane, and allowed to dry. The Examiner admits that Chu fails to teach the surface active agent having a sugar in hydrophilic part.

The Examiner also relies on Jobling et al., taking the position that the reference discloses test strips and a process of manufacturing test strips, where the strip comprises a porous material comprising a test zone (reactive layer) having immobilized specific binding components (reactive components). The Examiner states that Jobling et al. disclose that a solution comprising Tween 20 (surfactant) is applied to the porous strip and dried. Jobling et al. fail to teach the surface active agent recited in Applicants' claims.

The Examiner now relies upon Shigehiro as disclosing immunoassays, and teaching the addition of a non-ionic surface active agent having a disaccharide chain at a hydrophilic part to a reagent for the immunoassay. The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the surface active agents such as taught by Shigehiro into the analytical device and method of Chu, or the method of Jobling et al., because Chu and Jobling et al. specifically teach that surfactants can be used, and Shigehiro teach that the addition of surface active agents having a disaccharide chain at a hydrophilic part provides for improved assay sensitivity.

Regarding claim 49, the Examiner admits that Chu, Jobling et al., and Shigehiro fail to teach that the reactive layer is dried by freeze drying. The Examiner relies on Iwata et al. only to teach freeze drying.

Applicants' Arguments

Applicants respectfully disagree with the Examiner's position for the following reasons.

As discussed above, neither of the primary references (Chu or Jobling et al.) teach or suggest Applicants' recited surface active agent. The Shigehiro reference is relied upon by the Examiner to [allegedly] remedy this deficiency.

Shigehiro discloses adding a nonionic surface active agent having a disaccharide chain at a hydrophilic part to a reagent for immunoagglutination test, in order to enhance the reaction sensitivity by suppressing the non-specific reactions. Shigehiro mentions n-dodecyl-β-D-maltoside, n-nonyl-β-D-thiomaltoside, sucrose monocaprate, and sucrose monolaurate as concrete examples of a nonionic surface active agent having a disaccharide chain at a hydrophilic part.

The Examiner appears to take the position that it would be possible to obtain the same construction and effect of Applicants' invention, i.e., the improvement of preservation stability, by applying the surface active agents of Shigehiro to the teachings of Chu or Jobling et al.

However, the primary effect of Shigehiro is that the sensitivity of the reaction itself can be improved by adding a nonionic surface active agent having a disaccharide chain at a hydrophilic part to a liquid phase reaction system. While Shigehiro does not provide the principle of improving the sensitivity by adding the above-mentioned surface active agent, it is clear that Shigehiro relates to a homogeneous assay field based on the description on page 2, paragraph [0006], which states, "condensation methods, such as latex, are homogeneous immunoassays in which a sample ingredient exists at the time of an antigen-antibody reaction, and high sensitivity-ization has increase of a nonspecific reaction." Thus, the reference teaches that increase of sensitivity is inextricably linked to an increase of a nonspecific reaction. This passage further states, "[v]arious sensitizers actually reported … for example, a polyethylene glycol, dextran, etc., … mention … although [being] effective in … raising the sensitivity of an antigen-antibody reaction, … had the fault of also … simultaneously [increasing] a nonspecific reaction."

In contrast, Applicants' invention relates to a heterogeneous assay, which is quite distinct from the homogeneous assay of Shigehiro. Please see page 7, lines 5-12 of the original specification, which states, "a chromatography specimen which is obtained by laminating plural wettable porous materials or made of a single-layer porous material, in which a reactive layer on which at least one of reactive components adopted in a chromatographic analysis is immobilized

includes a surface active agent having such a property that it can be solidified when dried."

Improving the sensitivity in the homogeneous assay field, which does not require binding/free (hereafter "*B/F*") separation, cannot directly correlate to improving the sensitivity in the heterogeneous assay field, which does perform a *B/F* separation. Though Shigehiro substantiates and teaches that the sensitivity is improved by using the above-mentioned surface active agents with showing various reaction examples, each of the examples relate to the homogeneous assay.

An antigen-antibody reaction is a binding reaction between an antigen and an antibody. The principle of the homogeneous assay is based on detecting the binding reaction signal in a state where unreacted and unbound antigen and antibody coexist. Thus, there are inherent problems, such as occurrence of noises derived from unreacted antibody and antibody labeled substances. More specifically, in a homogeneous assay where the latex particles disclosed in Shigehiro are used as labeled substance, even if no antigen-antibody reaction occurs, the same number of latex particles exist in the reaction system. Meanwhile, in a case where an antigen-antibody reaction does occur, the same numbers of latex particles still exist. In this case, though the signal change caused by agglutination reaction can be captured, a signal is generated due to that the latex particles which do not practically relate to the agglutination reaction coexist, thereby generating a so-called noise.

On the contrary, if the heterogeneous assay using the latex particles is assumed, the latex particles which are not involved in an antigen-antibody reaction are eliminated by *B/F* separation. Thus, the signals which are caused only by the bound latex particles in the antigen-antibody reaction could be finally detected, and the signals caused by unreacted latex particles (which would become noise) are substantially eliminated.

As discussed above, the basic principle (or the technical problem) for the homogeneous assay and the heterogeneous assay are quite different. Thus, the mere fact that Shigehiro improves the sensitivity by solving the inherent problem in the homogeneous assay (by providing a link between the sensitivity enhancement and the increase in the nonspecific absorption) is quite irrelevant to the heterogeneous assay.

Thus, Applicants respectfully assert that one of ordinary skill in this art would not look to the teachings of Shigehiro to remedy the deficiency of the primary references (Chu and Jobling et al.).

Further, as Applicants have previously asserted, the surface active agent has various characteristics based on its chemical nature such as washing, foaming, emulsifying, permeating, solubilizing, dispersing, emolliating, retarding, spreading, sterilizing, and antistaticing. The effect of Shigehiro seems to be brought about by some of the above problems.

Applicants' invention enhances the solubility and enhances the permeability by a function of sugar, while it reduces the influences on proteins, thus minimizing denaturation or deactivation of immobilized specific protein. Thus, Applicants' invention achieves the enhancement of preservation stability, the lengthening of the quality preservation period, and the relaxation of the maintenance condition of a chromatography specimen.

As discussed above, the teaching of Shigehiro, which describes the reaction sensitivity enhancement in a homogeneous assay, cannot provide motivation for a substitution in the heterogeneous assay field. Accordingly, Applicants respectfully assert that one of ordinary skill in the art would not have looked to Shigehiro to remedy the deficiencies of Chu and Jobling et al., in order to arrive at Applicants' invention. Thus, the combination of references is improper.

Furthermore, as Iwata et al. was only relied upon to teach freeze drying, this reference also fails to remedy the deficiencies of the above-discussed combinations of references.

For these reasons, the invention of Applicants' claims is clearly patentable over the cited references. It is respectfully requested that the rejections be withdrawn.

Conclusion

Therefore, in view of the remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this response, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

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